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Stereochemistry and total synthesis of janolusimide, a tripeptide marine toxin

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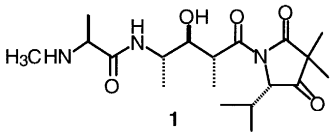
Abstract

The stereochemistry of janolusimide, a lipophilic tripeptide marine toxin, has been fully elucidated by stereoselective synthesis of the lactam component (5*S*)-3,3′-dimethyl-5-isopropylpyrrolidin-2,4-dione. The peptide was then synthesized in 13 steps and in 0.8% total yield.

Keywords: marine metabolites; molluscs; peptides; imides.

Several unusual peptides endowed with interesting biological activities have been isolated from marine organisms.[1] Some of them have been synthesized both for their interesting biological activities and in order to prove (or disprove) structure and stereochemistry.[2]



1

Janolusimide (**1**) is a lipophilic tripeptide neurotoxin isolated from the nudibranch mollusc *Janolus cristatus*.[3] From a structural point of view, **1** is a unique peptide since, besides *N*-methyl-L-alanine, it contains two rather unusual constituents, a 4-amino-3-hydroxy-2-methylpentanoic acid and a previously undescribed lactam, the latter being linked to the remaining part of the molecule by means of a labile imide linkage. Moreover, the other naturally occurring peptide having a 4-amino-3-hydroxy-2-methylpentanoic acid constituent is the antitumor antibiotic bleomicin A_2[4] in which the amino acid occurs as the 2*S*,3*S*,4*R* isomer.

In the paper describing the gross structure of janolusimide,[3] only the stereochemistry of *N*-methyl-L-alanine was established, while the stereochemistry of the other two constituents remained to be elucidated. Recently,[5] in the course of a synthesis of four stereoisomers of 4-amino-3-hydroxy-2-methylpentanoic acid, the stereochemistry of the amino acid occurring in janolusimide was established

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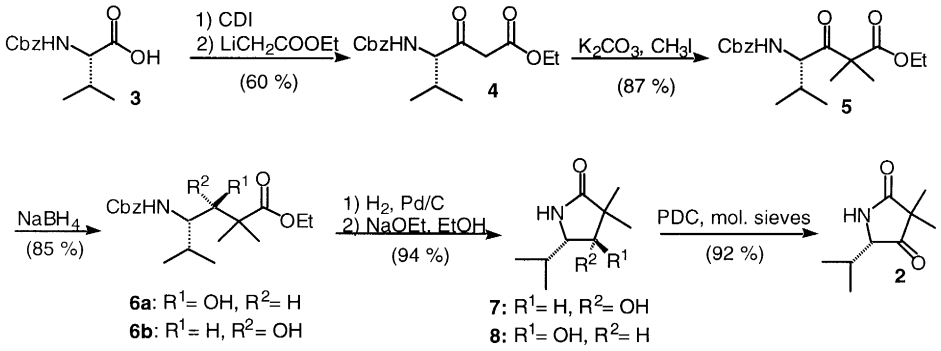
to be 2*R*,3*S*,4*S*. We report here the elucidation of the absolute configuration of the lactam portion (**2**) which establishes the complete stereochemistry of janolusimide to be **1**, as well as the total synthesis of the tripeptide.

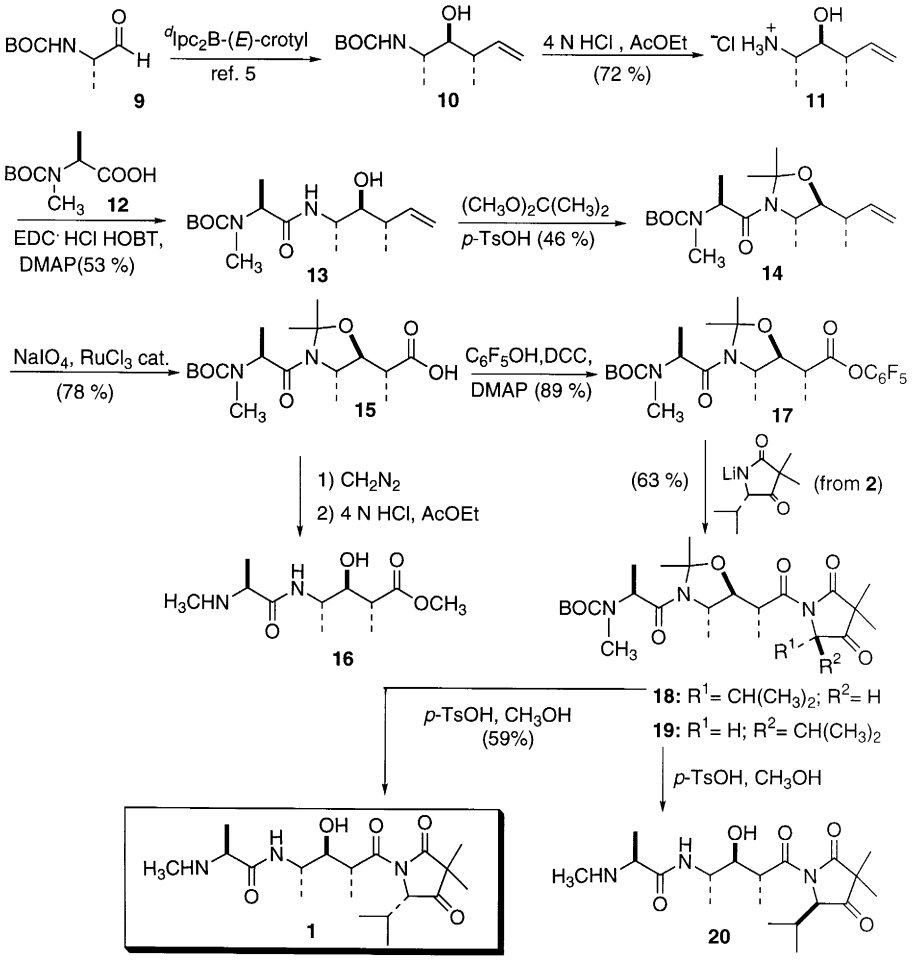
In order to elucidate the stereochemistry of the single stereogenic center in the lactam ring, we decided to synthesize the *S*-isomer **2** starting from L-valine (Scheme 1). The carboxyl group of *N*-carboxybenzyl-L-valine (**3**) was activated by means of 1,1′-carbonyldiimidazole (CDI) and the resulting adduct was reacted in situ with the carbanion generated from butyllithium and ethyl acetate to afford the β-ketoester **4**,[6] $[\alpha]_D$ −29.8; c 0.3, CH_2Cl_2 (lit.[6b] $[\alpha]_D$ −28.7; c 1.22, CH_2Cl_2), in 60% yield. Alkylation of **4** was carried out with methyl iodide and potassium carbonate, using less than the required stoichiometric amount of base in order to avoid racemization of the resulting product. The optically active dimethyl derivative **5**, $[\alpha]_D$ −4.4 (c 3.9, $CHCl_3$), was obtained in 87% yield. In order to avoid racemization of **5** during the deprotection–cyclization step,[7] **5** was reduced with $NaBH_4$ to a chromatographically separable mixture of diastereomers **6a** and **6b** (ca. 1:1) which were deprotected and cyclized to the diastereomeric hydroxylactams **7** and **8**.[8] Oxidation of the **7** and **8** mixture with PDC in the presence of molecular sieves[9] afforded **2**, whose optical rotation ($[\alpha]_D$ −30.5; c=0.3, $CHCl_3$; natural **2**[3] $[\alpha]_D$ –38.3; c=0.7, $CHCl_3$) establishes the absolute configuration of the lactam occurring in janolusimide and of the tripeptide itself as depicted in **1**.



Scheme 1.

The introduction of the central amino acid with the desired stereochemistry into the growing janolusimide molecule was carried out via the alkene **10** which was prepared following the recently described procedure[5] (Scheme 2). Thus, *N*-BOC-L-alaninal (**9**), prepared by reduction of *N*-BOC-L-alanine methyl ester,[10] was reacted with the organoborane reagent prepared from (−)-B-methoxydiisopinocampheylborane and (*E*)-2-butene[11] to afford the homoallylic alcohol **10**. Deprotection of **10** afforded the aminoalcohol **11** which was coupled with *N*-BOC-*N*-methyl-L-alanine (**12**) using EDC[12] as the coupling reagent. The resulting product **13** was protected as the *N*,*O*-acetonide derivative (**14**)[13] which, in turn, was oxidized with $RuCl_3/NaIO_4$[14] to the protected dipeptide **15**.[13] Compound **15** was methylated with CH_2N_2 and deprotected (*p*-TsOH, CH_3OH) to afford **16** which was identical to the dipetide methyl ester obtained from degradation of the natural product.[3]

Coupling of **15** with the lactam **2** proved to be difficult. After several attempts, **15** was transformed into the pentafluorophenyl ester **17**[13,15] which was reacted with the *N*-anion obtained from **2** and butyllithium affording two diastereomeric protected tripeptides **18**[13] and **19**[13] in a 2.8:1 ratio and in 63% yield. Apparently, the conditions used for the preparation of the imidate (*n*-BuLi) caused partial racemization of **2**. Compounds **18** and **19** were separated by repeated silica gel chromatography and deprotected to afford janolusimide **1** (from **18**), ($[\alpha]_D$ −8.5; c=0.8, $CHCl_3$; lit.[3] $[\alpha]_D$ –10.3; c=2.5, $CHCl_3$) and its epimer **20** (from **19**). The identification of the deprotection product coming from **18** as **1** was made on the basis of



Scheme 2.

a mixed proton NMR spectrum of the synthetic compound with the natural one, since small differences in the chemical shift values were observed for the individual samples, as previously esperienced for the 4-amino-3-hydroxy-2-methylpentanoic acids.[5]

Acknowledgements

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